Mitotic Inhibitors

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Inhibition of mitosis is a validated treatment approach for non-small cell lung cancer (NSCLC). Both paclitaxel and docetaxel are approved by the Food and Drug Administration for the treatment of NSCLC, and many additional agents are currently being evaluated. The session began with Dr. Jim Winkler from ARRAY Biopharma providing background on mitotic inhibition. He broke the drugs into four categories, including several agents that were discussed in individual presentations (denoted by parentheses).

1. Microtubilin binders:
   a. Taxanes (including nab-paclitaxel)
   b. Epithelones (including ixabepilone)
   c. Halichondrins (including eribulin)
2. Microtubulin enzyme inhibitors: this class was not discussed further during the session, but these agents prevent spindle function, leading to mitotic arrest and cell death. Because some of these enzymes are not expressed in nerve cells, these agents could potentially avoid the neuropathy seen with taxanes.[1] Drugs in development include ARQ 621, EMD 534085, and LY2523355.
3. Mitosis checkpoint kinase inhibitors (including LY2603618).
4. Mitosis enzymes inhibitors (including aurora kinase inhibitors and polo-like kinase [PLK] inhibitors). These kinases have overlapping but different functions.[2]

Summary of Presentations

Dr. Amir Onn presented data on nab-paclitaxel in which paclitaxel is suspended in human serum albumin diluted in saline. Compared with cremaphor-based paclitaxel, the infusion time is shorter and steroids or antihistamines are not required (although recently, rare hypersensitivity reactions have been reported). The drug is being evaluated in many histologies and is approved by the Food and Drug Administration for treatment of breast cancer. A phase III trial in which carboplatin plus nab-paclitaxel was compared with carboplatin plus cremaphor-based paclitaxel was presented at ASCO 2010.[3] Despite a greater paclitaxel dose intensity in the nab-paclitaxel arm, the safety profile was generally more favorable. Response rate favored the nab-paclitaxel group, particularly in patients with squamous cell carcinoma (relative risk 1.67: confidence interval 1.26, 2.21).

Dr. David Spigel discussed the microtubule stabilizing epithelone B analog ixabepilone. Xenograft data show the ability of ixabepilone to overcome the resistance to taxanes seen in tumors overexpressing βIII tubulin.[4] Ixabepilone demonstrated activity in taxane-resistant NSCLC in a phase II trial.[5] It has been tested as a single agent, in combination with carboplatin, and in combination with bevacizumab. Nevertheless, a large phase II trial failed to show superiority of carboplatin and ixabepilone compared with carboplatin and paclitaxel, even in a subset of βIII tubulin-positive patients.

Dr. Joseph Aisner presented data on eribulin, a synthetic analog of halichondrin B. Suppression of microtubule polymerization and sequestration of tubulin into nonfunctional aggregates is the proposed mechanism of action.[6] A phase IB trial in combination with carboplatin defined the maximum tolerated dose as 1.1 mg/m^2 before carboplatin AUC 6. Responses were seen in prostate cancer and tonsillar cancer patients. At the time of the presentation, the study was in a dose expansion phase in chemotherapy-naive NSCLC patients.[7] Eribulin has also been studied in combination with erlotinib and pemetrexed.

Dr. Philip Bonomi discussed inhibitors of aurora kinases, serine threonine kinases that play key roles in mitosis. Aurora kinase A functions include roles in centrosome function, mitotic spindle assembly, telomerase up-regulation and ras, and nuclear factor-κB activation. Inhibition leads to mitotic delay, monopolar spindles, and chromosomal segregation errors. MLN8237 and ENMD-0276 are Aurora kinase A inhibitors in development. Aurora kinase B (AKB) associates with centromeres and along chromosomes. AKB is involved in the cytokesis process and associates with passenger proteins, including survivin, borealin, and internal centromere protein. Inhibition leads to polyploidy, particularly tetraploidy, and cell death. AZD1152 and GSK1070916A are AKB inhibitors in development. Pan-aurora inhibitors in development include PHA-739358, SNS-314, CYC116, PF-03814735, AT9283, and AS703569. Toxicities include myelosupression and mucositis.

Dr. Quincy Chu discussed PLK inhibitors. PLK2 and PLK3 are felt to have tumor suppressor qualities, but the relevance of these proteins is less clear than PLK1, the focus of the talk. PLK1 is a serine-threonine kinase overexpressed in many malignancies, including NSCLC. PLK1 is expressed throughout the cell cycle, but it is highest during M phase. PLK1 maintains genomic stability during S phase and is important for recovery from G2/M arrest because of DNA damage. PLK1 negatively regulates the activity and stability

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of p53 through phosphorylation. PLK1 inhibition leads to proteasome-mediated degradation. Preclinical synergy has been shown with pemetrexed, gemcitabine, and cisplatin. Dr. Chu specifically discussed BI 6727, a dihydropteridinone derivative that binds the ATP-binding pocket. Nanomolar range IC50 was seen, whereas there was no inhibition of 50 other kinases up to 10 μM. In clinical trials, responses have been seen with myelosuppression as the main toxicity.

Dr. Eric Westin discussed the development of LY2603618, an ATP-competitive checkpoint kinase 1 inhibitor. In vitro, the agent impairs DNA synthesis, increases DNA damage (via mitotic defects), and induces apoptosis. In xenograft models, LY2603618 impedes tumor growth when given in combination with pemetrexed. A phase I study established 150 mg/m^2 as the maximum tolerated dose along with pemetrexed 500 mg/m^2 every 3 weeks. LY2603618 was given 1 week before the first dose of pemetrexed and then the day after pemetrexed with each cycle. One partial response was seen, and a phase II study in NSCLC is ongoing.

Future Directions

Several speakers specifically addressed future directions during their talks. Dr. Onn discussed the potential for coadministration of tumor-penetrating peptides with nab-paclitaxel[8] and selecting patients based on sparc, a protein that binds to albumin and has been considered as a potential predictor of response.[9] Dr. Aisner discussed a planned phase III trial of eribulin and gemcitabine versus cisplatin and gemcitabine. Dr. Chu discussed a planned randomized phase II trial of BI 6727, pemetrexed, or the combination of the two agents in second- or third-line NSCLC.

In this session, several agents in development were reviewed. These agents act on the mitotic process, a proven target for antineoplastic therapy. It will be important for the development of these agents to evaluate the potential advantages over available mitotic inhibitors. It is likely that patient selection will hold a key to improving the therapeutic window by enhancing efficacy and/or limiting toxicity.

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